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# One-Pot Synthesis of Polyaza[n]naphthalenophanes and Polyaza[n]anthracenophanes.

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***Abstract***: Pernosylated polyaza[n]cyclophanes ***13-20*** were prepared by a Richman-Atkins modified methodology. Deprotection under mild conditions gave polyaza[n]cyclophanes ***21-28***. This methodology allows for the preparation of cyclophanes containing labile C-N bonds.


The Richman-Atkins cyclization reaction represents one of the most general approaches for the preparation of polyaza macrocycles.[1] In this procedure, a pertosylated polyamine is reacted, under basic conditions, with a dihalide to give high yields of the pertosylated macrocyclic structure even if high dilution conditions are not used. The tosyl group seems to play several important roles in this reaction, protecting the secondary amino groups and, at the same time, increasing the acidity of the remaining N-H bond of the primary amino groups so that deprotonation is easily accomplished even with relatively weak bases. On the other hand, the bulky nature of this group is, most likely, involved in a preorganization of the intermediates which favors the transition state leading to the intramolecular cyclization, decreasing the importance of the alternative intermolecular oligomerization processes. Additionally, the starting pertosylated polyamines are easily prepared, and most of the intermediate products are crystalline or solid compounds that can be easily handled and purified.

The main drawback of the use of the tosyl group for the N-protection is the rather drastic conditions needed for deprotection. This is of importance when other functional groups are to be present in the final structure or for macrocycles containing labile C-N bonds. This has led to the search for other N-protecting groups that could be used for the Richman-Atkins reaction. Several examples of tosyl group substitutes, such as mesyl, trifluoroacetyl, diethoxyphosphoryl..., have been reported.[2] However, most of those groups have not found general application as they also require deprotection under drastic conditions, the starting materials are prepared much less easily or the efficiency of the cyclization step is heavily decreased.

Recently, the use of the nosyl group (2- or 4-nitrophenylsulfonyl) for the protection of primary amino groups and its removal under very mild conditions has been reported.[3] As a matter of fact, the use of the nosyl group as a selectively removed protecting group has been described for the generation of molecular diversity in *N*-functionalized pyridinophanes.[3b,c] This has prompted us to study the use of this group as an alternative to the tosyl group in the Richman-Atkins reaction, according to *Scheme 1* and *2*. This is of particular interest for the preparation of macrocycles, such as polyaza[n](1,4)naphthalenophanes and polyaza[n](9,10)anthracenophanes,

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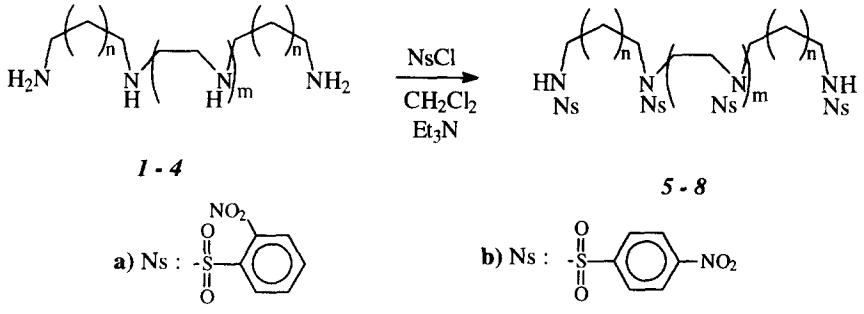
which contain labile C-N bonds that are cleaved under the usual deprotection conditions required for the tosyl group.




*Scheme 1*

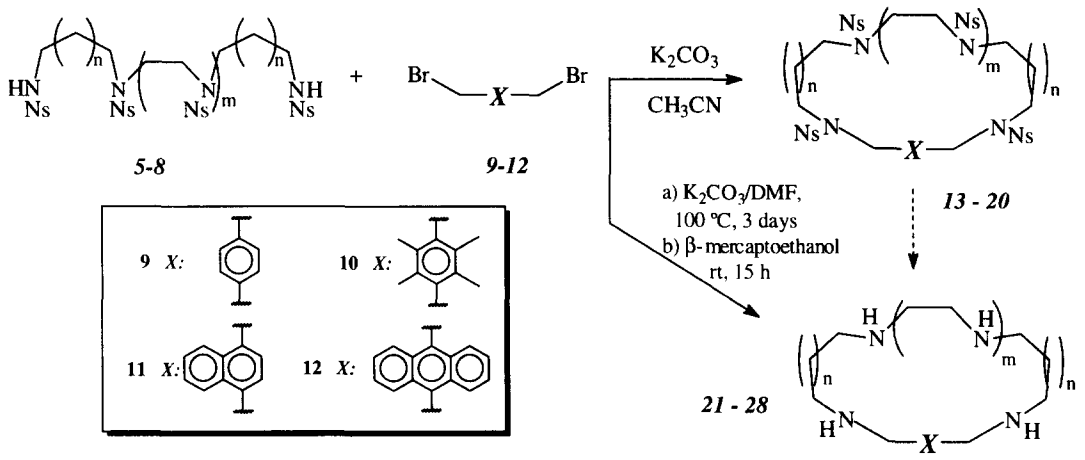
*Table 1. Yields Obtained in the Preparation of Pernosylated Polyamines*

| starting polyamine[a] | n | m | product | yield(%) |
|---|---|---|---|---|
| **1** | 0 | 0 | **5a** | 61 |
| | | | **5b** | 81 |
| **2** | 1 | 0 | **6a** | 54 |
| | | | **6b** | 63 |
| **3** | 0 | 1 | **7a** | 53 |
| | | | **7b** | 62 |
| **4** | 1 | 1 | **8a** | 74 |
| | | | **8b** | 86 |

a) all polyamines are comercially available.

Reaction of the corresponding polyamines (***1-4***) with 2- or 4-nitrophenylsulfonyl chloride in $CH_2Cl_2$ containing $Et_3N$ for 30 h gave the expected *N*-nosylated polyamines (***5-8***) in good yields (Table 1) as yellow solids sparingly soluble in most solvents. Reaction of compounds ***5-8***, under basic conditions with the appropiate dibromides (***9-11***) yielded the polyaza macrocyclic species of general structure ***13-20***.

Different *bis*(bromomethyl) arenes were selected for the cyclization reaction in order to obtain polyaza macrocycles containing relatively labile benzylic C-N bonds. The reaction conditions used were similar to those that had been used by us for the preparation of polyaza[n]paracyclophanes and related systems.[4] Accordingly the reaction was carried out in refluxing $CH_3CN$ using anhyd. $K_2CO_3$ as the base. Concentrations of both reactants were maintained in the 1-$5x10^{-3}$ mol $L^{-1}$ range for all experiments. Results obtained show that the efficiency of this process is comparable to that found when pertosylated polyamines were used and some of them are gathered in Table 2.




*Scheme 2*

*Table 2.- Yields Obtained for the Richman-Atkins Cyclization of Pernosylated polyamines*

| pernosylated polyamine | dibromide | product | yield(%)[a,b] |
|---|---|---|---|
| **5b** | **11** | **13b** | 92 (98) |
| **5b** | **12** | **14b** | 75 (99) |
| **6b** | **12** | **15b** | 84 (95) |
| **7a** | **12** | **16a** | 94 (84) |
| **7b** | **11** | **17b** | 88 (92) |
| **8a** | **11** | **18a** | 98 (75) |
| **8b** | **11** | **18b** | 90 (75) |
| **8b** | **12** | **19b** | 87 (70) |
| **8b** | **9** | **20b** | 78 (90) |

a) yields calculated for the isolated product. b) cyclization yields obtained for pertosylated polyamines are given in parentheses. See ref. 4.

Denosylation of macrocycles ***13-20*** to give the free bases ***21-28*** was studied using the different thiol nucleophiles described in the literature (PhSH, $HSCH_2COOH$, $HSCH_2CH_2OH$). In general, yields obtained were low and C-N cleavage at the naphthylic or anthrylic position was not completely suppressed. The low solubility of the pernosylated macrocyclic compounds was considered an important drawback in this process, and, accordingly, a different one-pot approach was assayed. Thus, starting from *o*-pernosylated polyamines cyclization was carried out in $DMF/K_2CO_3$ at 100°C for three days. The resulting mixture was cooled, the sulfur nucleophile was added and stirring at rt was continued for 15 h. In this way, using $HSCH_2CH_2OH$ as the nucleophile, the expected polyazacyclophanes could be isolated in the yields given in *Table 3*. For simple compounds such as ***28*** yields were lower those obtained when the tosyl group was used (38% overall yield for a two step process).[4a] Important differences, however, were observed for 1,4-naphthyl and 9,10-anthracenyl derivatives ***21-27***. Only two naphthyl derivatives had been up to now obtained in very low yields (<5%) from the pertosylated derivatives with the use of HBr/AcOH/PhOH, in isolated experiments not easily reproduced.

Polyaza[n](9,10)anthracenophanes had not been synthesized before from the corresponding pertosylated macrocycle, as all attempted detosylations, carried out under a variety of conditions did always afford products derived from C-N cleavage at the benzylic positions, 9,10-dimethylanthracene being the major product isolated.[4c]

Thus, the mild conditions required for deprotection of the nosyl group allow the one-pot preparation of products that cannot be obtained when the tosyl group is used. Further work is in progress in order to study the scope of the use of the nosyl group in this field, as well as to analyze the use of related groups and modifications in the reaction conditions.

*Table 3. Yields Obtained for the One-Pot Preparation of Polyaza[n]naphthalenophanes and Polyaza[n] anthracenophanes*

| pernosylated polyamine | dibromide | product | yield(%)[a] |
|---|---|---|---|
| **5a** | **11** | **21** | 18 |
| **5a** | **12** | **22** | 27 |
| **6a** | **11** | **23** | 13 |
| **6a** | **12** | **24** | 25 |
| **7a** | **12** | **25** | 12 |
| **8a** | **11** | **26** | 28 |
| **8b** | **12** | **27** | 27 |
| **8b** | **10** | **28** | 11 |

a) overall yield for the isolated product after purification.

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## REFERENCES

1. Richman, J.E.; Atkins, T.J. *J. Am. Chem. Soc.* **1974**, *96*, 2268-2270.
2. a) Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*; Wiley: New York, **1991**. b) Qian, L.; Sun, Z; Mertes, M.P.; Bowman-Mertes, K. *J. Org. Chem.* **1991**, *56*, 4904-4907. c) Pratt, J.A.E.; Sutherland, I.O.; Newton, R. *J. Chem. Soc., Perkin Trans 1* **1988**, 13-22.
3. a) Fukuyama, T; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373-6374. b) An, H.; Cook, P.D. *Tetrahedron Lett.* **1996**, *37*, 7233-7236. c) An, H.; Cummins, L.L.; Griffey, R.H.; Bharadwaj, R.; Haly, B.D.; Fraser, A.S.; Wilson-Lingardo, L.; Risen, L.M.; Wyatt, J.R.; Cook, P.D. *J. Am. Chem. Soc.* **1997**, *119*, 3696-3708. d) Miller, S.C.; Scanlan, T.S. *J. Am. Chem. Soc.* **1997**, *119*, 2301-2302. e) Wipf, P.; Henninger, T.C. *J. Org. Chem.* **1997**, *62*, 1586-1587. f) Piscopio, A.D.; Miller, J.F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143-7146. g) Russell-Bowman, W.; Coghlan, D.R. *Tetrahedron* **1997**, *53*, 15787-15798.
4. a) Bencini, A.; Burguete, M.I.; García-España, E.; Luis, S.V.; Miravet, J.F.; Soriano, C. *J. Org. Chem.* **1993**, *58*, 4749-4753. b) Burguete, M.I.; Escuder, B.; García-España, E.; Luis, S.V.; Miravet, J.F. *J. Org. Chem.* **1994**, *59*, 1067-1071. c) Altava, B.; Burguete, M.I.; Escuder, B.; Luis, S.V.; García-España, E.; Muñoz, M.C. *Tetrahedron*, **1997**, *53*, 2629-2640.